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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region D1418B

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 331-2904

January 27, 1998

WARNING LETTER

RELEASE

REVIEWED BY _____ C.O. _____ DATE

CERTIFIED MAIL
RETURN RECEIPT REQUESTED
Patrick J. Zenner, President & CEO
Hoffmann-LaRoche, Inc.
340 Kingsland Street
Nutley, New Jersey 07110

FILE NO.: 98-NWJ-02

Dear Mr. Zenner:

During an inspection of your facility located at 340 Kingsland Street, Nutley, New Jersey, between the dates of July 16 and August 25, 1997, our investigators documented serious deviations from the current good manufacturing practice regulations (Title 21, Code of Federal Regulations, Part 210 and 211) in conjunction with your firm's manufacture of prescription drugs.

These deviations were presented to your attention on an FD-483 List of Observations at the close of the inspection on August 25, 1997. The CGMP deficiencies cause your products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

The significant observations are as follows:

1. The initial investigation, QMPC 005-97 into a large amount of an impurity present at a retention time of [redacted] minutes ([redacted]) for HSA-Free Roferon-A Injection lot 2003-08096 at the six month stability station was inadequate. [redacted] batches of HSA-Free Roferon-A Injection on hold were released after the investigation had determined that several unidentified, unrelated impurities at retention times of [redacted], approximately [redacted] and approximately [redacted] minutes were present and have been present at some levels in all batches of Referon-A. Referon-A batches [redacted] and [redacted] were released prior to identifying these impurities. These peaks for lots 2003-08096 and 0004-02177 were found at levels higher than the firm's specification of maximum [redacted] of Mf1 for other related impurities.

In addition, the initial investigation (report initiated 2/7/97) and a memo from Hoffman LaRoche to CBER dated 3/17/97, incorrectly ruled out cleaning agents as a source of the unidentified, unrelated impurities in Referon-A lot 2003-08096. This incorrect information was forwarded to CBER. An Addendum to investigation QMPC 005-97 (report initiated 7/21/97) concluded that the cause of the impurities was a disinfectant found in Lysol cleaning agent (2-phenylphenol & 2-benzyl-4-chlorophenol).

2. The process validation for Bactrim Pediatric Suspension (Trimethoprim, 40 mg. & Sulfamethoxazole 200 mg/ml) is inadequate. For example:

   a. No established mixing speeds or times during compounding. Additionally, no established mixing speeds for agitation of the bulk suspension in the storage tank prior to and during filling.

   b. There is no microbiological evaluation of the active pharmaceutical ingredients, several excipients, physical components (bottles & capsules), environment, and the effectiveness of the cleaning/sanitization.

   c. Temperatures during compounding were not specific and were not recorded in the batch record.

   d. No data to support the fill volume range of [redacted] ml (+) or (-) [redacted] during the filling of 16 oz. bottles.

3. The bulk suspension time study for Bactrim Pediatric Suspension, to support the 30 day storage time frame prior to filling, was inadequate in that there was no microbiological evaluation of the bulk suspension.

4. Process validation of Bactrim Pediatric Suspension was not conducted to support the use of Hoffmann-LaRoche, Nutley, (a new source) produced Trimethoprim, active pharmaceutical ingredient. This new source (HLR) of the raw material has a different particle size than the [redacted] produced Trimethoprim.

5. The process validation for Bumex Injection (Bumetanide) 0.25 mg/ml is inadequate in that there is no data to support the [redacted] overage incorporated into the compounding and filling processes.

6. The steam sterilization cycle for the empty syringes used for the filling product is not validated. During the validation process the following occurred: the first set of biological challenge runs, 6 (six) out of 7 (seven) runs were positive for growth of the challenge organism Bacillus stearothermophilus. The positive growth was attributed to problems with the inoculation procedure for the needle shields by the Quality Control Microbiology Laboratory. During the second set of runs, 2 (two) out of 7 (seven) runs were positive for growth. The positive growth was attributed to the high jacket pressure of the autoclave. The third set of runs were made with adjustments to the jacket pressure. One out of the 5 (five) runs was positive for growth. After an inconclusive investigation, one additional run was made and no growth was found. It was concluded by the Production and Quality Units that the process is validated. None of the initial 3 (three) sets of runs met the acceptance criteria outlined in the validation protocol which indicates a complete destruction of the challenge organism.

7. The compounding and filtration areas which are utilized for the manufacture of sterile drug products and are designed to meet class 100,000 conditions have not been qualified. Air changes, pressure differentials and viable & non viable particle monitoring have not been conducted.

8. The firm's standard operating procedure (SOP) PNUQC-050-004 entitled, Labeling and Dating Reagent Chemical, Solvents, and Solutions is inadequate in that it does not require any solution (e.g. mobile phase) which will be entirely used during testing to be labeled and dated.

9. No data to support the incubation time of [redacted] days for contact surface and slit to agar plates (the plates are used for environmental monitoring).

10. The growth confirmation testing is inadequate in that it is conducted on only one lot of purchased media per year and testing does not consist of all USP indicator organisms.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the good manufacturing practices regulations. Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. This includes seizure and/or injunction.

We remain concerned regarding the justification for your firm's family approach to validation and suggest that the approach be further discussed in any future meetings.

Any additional information you wish to submit should be sent to the Food and Drug Adminsitration, Parsippany, New Jersey, 07054 Attention: Andrew Ciaccia, Compliance Officer.

Very truly yours,

Douglas Ellsworth

DOUGLAS ELLSWORTH
District Director

AC:slw